Submitter Name: Sasha Fulton Submitter Email: slf2127@columbia.edu

Multi-omic single-nucleus characterization of orbitofrontal cortex after cocaine self-administration

Sasha Fulton[1,2] and Ian Maze[1]

[1]Icahn School of Medicine at Mount Sinai, New York, NY;
[2]Vagelos College of Physicians and Surgeons, Columbia University, New York, NY

Cocaine use disorder (CUD) involves persistent neuroadaptations in Orbitofrontal Cortex (OFC), a brain region critically involved in guiding reward-based decision making and motivated behavior. Aberrant hyperactivation in the OFC modulates compulsive drug-taking behaviors and cocaine relapse vulnerability in CUD, impairing the reward circuitry's capacity to self-regulate. This hyperexcitable state is driven by epigenetic regulatory mechanisms that maintain these activated states, leading to persistent deficits in the control of motivated behavior. Although OFC excitability might be clinically relevant in the development of treatments that might alleviate relapse vulnerability in CUD patients, there have been no studies to date examining the precise cell-type specific mechanisms involved in OFC dysfunction during chronic cocaine use**.** Here, we used an extended access cocaine intravenous self-administration (SA) model to profile both chromatin and transcriptional alterations in the OFC with multiomic single-nucleus RNA sequencing (snRNA-seq) and single-nucleus Assay for Transposase Accessible Chromatin (snATAC-seq). With this data set, we have identified specific cell types within the OFC that are preferentially disrupted after extended withdrawal from cocaine SAs. In addition, we have leveraged chromatin accessibility profiles to identify genomic regulatory elements, known as enhancers, that are exclusively open in specific OFC cell-types. Finally, by comparing chromatin structural changes following withdrawal from cocaine self-administration vs. saline controls, we have identified enhancers that are specific to extended cocaine withdrawal. These cocaine-specific enhancers will allow us to investigate how neuronal ensembles marked by stable chromatin reorganization contribute to the cellular and behavioral adaptations following cocaine experience. With these data, we will leverage these enhancer elements as genomic access points for targeted manipulation of defined cell-types in the OFC, as well as for cocaine-specific neuronal ensembles.